The Examiner rejected claims 9-17 "for the reasons of record in the office action of paper no. 14." Paper no. 14 stated that the invention was unpatentable over Harvey et al., U.S. patent 6,674,753, 1997, Partanen et al. (J. Occup. Med., 1994, vol. 36 pp 1324-1328) or Witters et al. (Clin. Cancer Res., 1995, vol. 1, pp. 551-557) in view of Graus-Porta et al. or Olayioye et al., and further in view of WO 94/11734 (Johansen et al., 1994).

The Examiner rejected Applicants' arguments that the cited patents (1) give disparate results, (2) have a more limited dynamic range, (3) do not teach quantification and (4) do not teach direct labeling of the antibodies. The Examiner stated that because Applicants' invention are a method of quantifying a receptor, not a method of diagnosis, that the unsuspected finding of a "decrease" of Applicants' invention, vis-à-vis the prior art. The Examiner failed to appreciate that the decrease shows a different mechanism of operation thereby highlighting how the prior art teaches away from the present invention, both by operation and combination, and the non-obvious nature of Applicants' invention although, according to the Examiner, skill in the antibody area is high.

The Examiner stated that it would be obvious to use any antibody shown to have appropriate binding in a sandwich assay and to directly label the antibody with acridinium. However, what appears to be obvious conceptually is met by a number of practical unanticipated hurdles which the present invention has overcome.

Contrary to the assertion by the Examiner that the present invention would have been obvious to one skilled in the art, the present invention could not have been achieved without undue experimentation without reference to the present disclosure. As one skilled in the art knows, the development of a sandwich-type immunoassay encounters many unknowns in light of the limited knowledge of a particular set of antibodies to bind to a particular antigen with a known biochemical specificity. Such unknown factors, which must be resolved through experimentation include, but are not limited to: (1) an antibody that does not recognize an antigen in its native configuration in solution although it recognizes a denatured form; (2) buffer conditions that allow a primary antibody to bind an analyte of interest but do not permit the binding of the detector antibody; (3) binding of the analyte, when in bodily fluids, to other biological molecules that alter or mask the ability to quantify the molecule; and (4) unpredictable conformational changes caused by (a) binding of antibody to an analyte in solution which causes changes to the analyte that mask or block the epitope recognized by another antibody; (b) labeling the antibody with horseradish peroxidase, FITC or acridinium that directly or indirectly block the antigen-binding site rendering the antibody dysfunctional; and (c) attaching a primary antibody directly to a solid phase which inactivate its ability to bind to the analyte of interest. Thus, even for one highly skilled in the art of immunoassay design, it is not obvious which antibody combination, buffer conditions, solid phase and detection system will work for a particular analyte in a complex biological fluid. Each of the foregoing challenges was experienced for the present invention. Other combinations failed to produce an immunoassay characterized by a low detection limit, broad linear range, and good reproducibility although the biochemical properties would have suggested other combinations would result in such functionality.

Contrary to the Examiner's assertion that a direct comparison is not made between Applicants' invention and the prior art, Fig. 7B of Baron et al (1998) reflects a direct comparison with the Oncogene Research Products EGFR ELISA. The Examiner asserts that the Oncogene ELISA is used to detect breast cancer and Applicants' assay is used to detect ovarian cancer and thus one would not expect similar results. However, the Examiner failed to appreciate that both assays are used to detect EGFR. If both were detecting the identical biochemical entity, and one knows that both assays are designed to detect antigenic determinants of the EGFR's ECD, one would expect 100% concordance. Applicants' invention distinguishes between healthy women and those suffering cancer with a 95% specificity and a 64-81% sensitivity. In contrast, the Oncogene product does not distinguish between healthy men and women and those with cancer.

Further, the Examiner newly rejected claims 9-23 on the basis that the invention does not point out and distinctly claim the subject matter of the invention. The Examiner asserts that the invention detects both the full-length and soluble receptor. Applicants claim that their invention detects sEGFR in human bodily fluids. An ALISA has the ability to quantify full-length EGFR in cellular cytosols and tissue extracts, i.e., tissue samples containing whole cells, but full-length EGFR is not present in human body fluids. One skilled in the art would appreciate that distinction and thus the claims do distinctly claim the subject matter.

Finally, the Examiner rejected Claims 9-17 as being anticipated by Baron et al. (1998) and stated that the authors on the paper who are not listed as inventors would be deemed "others"

under MPEP 213(III). As the attached declaration under Rule 1.132 shows, the authors who are not listed as inventors did not contribute to the present invention and the publication reflects solely the work of inventors.

Further, the 1998 publication does not anticipate the present invention. When the 1998 publication issued, neither Applicants nor peers knew that aspects of the ALISA described therein would detect sEGFR ECD-containing moiety compared to other ELISA's previously developed with antibodies that bind to the ECD of EGFR. Specifically, at the time of publication, Applicants, and others in the field, believed that an ALISA having the attributes described in the 1998 paper would measure the same entity that the Oncogene Research Products ELISA measured and demonstrated 100% correlation in the sEGFR concentrations from the same serum samples taken from healthy subjects. Surprisingly, the ALISA-defined sEGFR ECD-containing moiety, as used in the present invention, discerns healthy women from high cancer patients with high test specificity and sensitivity. This is surprising because the ELISA does not have these properties. Demonstrating that healthy subjects and patients with cancer have different serum concentrations of a particular analyte is not sufficient for a biomarker test to be clinically useful, the test must also have high sensitivity, specificity, positive predictive value, negative predictive value and accuracy to be useful clinically. These attributes of the present invention are not anticipated by Baron et al or Partanen et al. In fact, Partanen et al, in which the context of the 1998 Baron paper was issued, teaches away from the present invention.

CONCLUSION

Applicants respectfully submit that the present invention is not obviated or anticipated by

the teachings and that the patent application and claims therein, as amended, are in a condition for allowance. Reconsideration is, therefore, respectfully requested.

Respectfully submitted,

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